Modeling chronic psoriatic inflammation in a 3D reconstructed skin

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Introduction: We have previously identified a model of psoriasis characterized by an over-activation of keratinocytes. This over-activation is due to an abnormal differentiation of keratinocytes. The presence and the migration of leucocytes through skin substitutes were examined thanks to anti-CD163 and CD1 stains. The expression level of specific cytokines and chemokines, such as MCP-1, IL-6, and IL-1β, were further assessed by ELISA and IHC.

Results: Our results showed that both macrophages and T cells were homogeneously dispersed throughout the dermis. Macrophages incorporated into healthy substitutes appeared to modify the expression of early epidermal differentiation markers toward an inflammatory phenotype, such as observed with psoriatic cells. T cells affected early and late keratinocyte differentiation markers toward a psoriatic phenotype. Moreover, expression levels of pro-inflammatory cytokines increased in healthy immunocompetent substitutes over time compared to immunodeficient models. Both innate and adaptive immune cells contribute to keratinocyte deregulation and these results strongly suggest that this unique immunocompetent model would be useful in the discovery of new therapeutic targets for the treatment of inflammatory chronic skin diseases, such as psoriasis.

Expression of sCD23 by Langerhans cells is required for Th17 differentiation and tethering of LC in the epidermis

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Langerhans cells (LCs) reside in the epidermis where they capture cutaneous antigens and migrate to the skin draining lymph nodes (sLN) to prime and differentiate T cells. Using a murine skin infection model, our group has recently demonstrated that Langerhans cells were both necessary and sufficient to drive T helper 17 (Th17) differentiation in response to epidermal Candida albicans infection in vivo. Th17 differentiation requires a combination of IL-1β, IL-6, IL-23 and TGFβ. LC-derived IL-6 but not IL-1β, IL-23 or TGFβ was required for Th17 differentiation. Although LC-derived TGFβ was not required for Th17 differentiation, we found that activation of latent TGFβ by the integrin αvβ8 expressed by LC was required for efficient Th17 differentiation during C. albicans infection. Notably, the constitutive absence of αvβ8 in LC, even in the absence of IL-6, was sufficient to block Th17 differentiation. A previous study has previously shown that activation of latent TGFβ by αvβ8 expressed by keratinocytes in 3D models is required to inhibit spontaneous migration of LCs from the epidermis to sLN. LC migration under steady state and inflammatory conditions, however, was not affected in αvβ8knockout mice. In contrast, tansomicin induced ablation of αvβ8 in 3D models prevented LC migration over time. LC were observed to be absent in the epidermis near the stratum granulosum and were significantly reduced from both the epidermis and sLN. Thus, activation of TGFβ by αvβ8 expressed by LC is required for efficient Th17 differentiation in the setting of C. albicans infection. αvβ8knockout mice are also required for appropriate epidermal localization of LC but this is likely compensated by other factors in the setting of a constitutive loss of this integrin.

Evaluation of soluble IgE receptors, sCD23, sFcRI and Galectin-3, in sera from patients with Bullous pemphigoid

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Bullous pemphigoid (BP) is one of many autoimmune diseases characterized by IgG autoantibodies that bind to BP-specific antigens and participate in the pathogenic mechanisms of BP. Several studies have reported the presence of soluble receptors in the circulation of BP patients that have been documented to have a role in the interaction with both membrane bound and soluble receptors. The goal of the current study was to evaluate circulating levels of all three soluble IgE receptors, sCD23, sFcRI and Galactin-3, in untreated BP patients and matched controls. Further, to better understand how these receptors might be involved in BP, soluble receptor levels were correlated with disease severity, circulating IgE and IgG autoantibody levels and peripheral eosinophil count. The study examined 39 patients with BP (24 females, 15 males, mean 78.2 years, range 59 - 97) and 38 healthy controls (21 female, 17 male, mean 78.4 years, range 64-98) with no history of infection. Serum samples were obtained from all patients and controls and sera were stored at -80 °C until analysis. ELISA was performed to measure serum levels of soluble CD23, FcεRI and Galactin-3. A one-way ANOVA was performed to compare the levels of each receptor between the groups. A matched paired t-test was used to determine if there was a correlation between the levels of each receptor and disease severity.

Type 1 interferon signaling suppresses the development of vitiligo as well as the response to melanoma immunotherapy

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Type 1 interferons, are cytokines originally recognized for their anti-viral properties. However, type 1 interferon signaling inhibits the development of vitiligo as well as the response to melanoma immunotherapy. We evaluated these effects by infecting melanoma cell lines with a Type 1 interferon-deficient lentivirus and then examining the effects on melanoma growth in vitro. We then characterized the effects of Type 1 interferon signaling on the immune response to melanoma using both functional and in vitro assays. Finally, we determined the effects of Type 1 interferon signaling on the response to melanoma immunotherapy using a murine model of melanoma.

Lupus Ro60 autoantigen cross-reactivity with commensal Ro60 orthologs

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Anti-Ro60 autoantibodies are some of the earliest found in lupus patients and initiate epitope spreading. Here we characterized a model of Type I interferon signaling-mediated cross-reactivity between Ro60 and Ro52, a skin microbiome commensal ortholog. Ro52 is required for efficient Th17 differentiation in response to epithelial infection, and has been hypothesized to be a unique immunocompetent model for the discovery of novel autoantigens. Both Ro52 and Ro60 were expressed in ortholog-specific mouse and human Ro52/Ro60 knockin models. Our results demonstrated that Ro52 cross-reactivity may initiate or flare lupus in genetically susceptible individuals. Subjects with systemic and subacute cutaneous lupus erythematosus and healthy controls were recruited and 16S V4 sequencing of the skin, oral, and fecal microbiomes was performed. The presence of commensals with Ro60 orthologs was common among healthy and lupus subjects. Ro60-lupus subjects had higher mean levels of P. propionibacterium on the skin than healthy subjects but there was no overall dysbiosis of the microbiota. Lupus memory T cell clones specific for B. thetaiotaomicron Ro60 proliferated in response to human Ro60, demonstrating T cell cross-reactivity. Human Ro60+ lupus serum immunoprecipitated P. propionibacterium Ro60 and its Y RNA binding partner, suggesting B cell cross-reactivity. Mice infected with a non-immunocompetent mouse anti-Ro60 antibody and cells from spleen and mesenteric lymph node proliferated in response to both B. thetaiotaomicron Ro60 and human Ro60, demonstrating cross-reactivity and the potential for causality. In summary, Ro60 autoimmune T and B cells from human lupus patients reacted with commensal Ro60 in vitro, and commensal Ro60 triggered anti-human Ro60 responses in vivo. Taken together, these data support that colonization with Ro60 ortholog-producing bacteria may induce and sustain chronic autoimmunity in lupus. This concept may apply more broadly to human autoimmune diseases and could lead to development of novel microbiota-targeted approaches to treat autoimmunity.